During rapid weight loss in obese children, reductions in TSH predict improvements in insulin sensitivity independent of changes in body weight or fat

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Abstract: BACKGROUND: Although serum TSH is often elevated in obesity and may be linked to disorders of lipid and glucose metabolism, the clinical relevance of these relationships remains unclear. SUBJECTS: Subjects were obese children and adolescents (n=206; mean age 14 yr) undergoing rapid weight and fat loss in a standardized, multidisciplinary, 2-month, in-patient weight loss program. DESIGN: This was a prospective study that determined thyroid function, glucose and lipid parameters, leptin, anthropometric measures, and body composition measured by dual-energy x-ray absorption at baseline and at the end of the intervention. RESULTS: At baseline, 52% of children had TSH concentrations in the high normal range (>2.5 mU/liter), but TSH was not correlated with body weight, body mass index sd scores, lean body mass, or body fat percentage. At baseline, independent of adiposity, TSH significantly correlated with total cholesterol (P=0.008), low-density lipoprotein cholesterol (P=0.013), fasting insulin (P=0.010), homeostatic model assessment (HOMA) (P=0.004), and leptin (P=0.006). During the intervention, mean body fat, TSH, HOMA, and fasting insulin decreased by 21, 11, 53, and 54%, respectively. Change (Δ) in TSH did not correlate with Δbody weight or Δbody composition, but ΔTSH significantly correlated with, Δfasting insulin and ΔHOMA, independent of Δbody weight or Δbody composition ($P<0.05$). CONCLUSION: TSH concentrations are elevated in obese children but are not correlated with the amount of excess body weight or fat. During weight loss, independent of changes in body weight or composition, decreases in elevated serum TSH predict decreases in fasting insulin and HOMA. These findings suggest interventions that target high TSH concentrations during weight loss in obese subjects may improve insulin sensitivity.

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During rapid weight loss in obese children, reductions in TSH predict improvements in insulin sensitivity independent of changes in body weight or fat

Short title: TSH and insulin sensitivity in obese children

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Precis: During weight loss, independent of changes in body weight or composition, decreases in elevated serum TSH predict decreases in fasting insulin and HOMA in obese children and adolescents.

Key words: TSH, insulin resistance, weight loss, children, body fat

Abstract

Background Although serum thyrotropin (TSH) is often elevated in obesity and may be linked to disorders of lipid and glucose metabolism, the clinical relevance of these relationships remains unclear.

Subjects Obese children and adolescents (n=206; mean age, 14 y) undergoing rapid weight and fat loss in a standardized, multidisciplinary, 2-month, in-patient weight loss program.

Design A prospective study that determined thyroid function, glucose and lipid parameters, leptin, anthropometric measures and body composition measured by DEXA at baseline and at the end of the intervention.

Results At baseline, 52% of children had TSH concentrations in the high normal range (> 2.5 mU/l) but TSH was not correlated with body weight, BMI-SDS, lean body mass or body fat percentage. At baseline, independent of adiposity, TSH significantly correlated with total cholesterol (p=0.008), LDL-cholesterol (p=0.013), fasting insulin (p=0.010), HOMA (p=0.004) and leptin (p=0.006). During the intervention, mean body fat, TSH, HOMA and fasting insulin decreased by 21%, 11%, 53% and 54%, respectively. Change in (Δ)TSH did not correlate with Δbody weight or Δbody composition, but ΔTSH significantly correlated with, Δfasting insulin and ΔHOMA, independent of Δbody weight or Δbody composition ($p<0.05$).

Conclusion TSH concentrations are elevated in obese children but are not correlated with the amount of excess body weight or fat. During weight loss, independent of changes in body weight or composition, decreases in elevated serum TSH predict decreases in fasting insulin and HOMA. These findings suggest interventions that target high TSH concentrations during weight loss in obese subjects may improve insulin sensitivity.

Introduction

Higher serum thyrotripin (TSH) concentrations are consistently found in obese children and adults compared to normal weight individuals (1-4). But the cause of the higher TSH concentrations in obesity, and whether they are an independent risk factor for disease, remains unclear. Some authors have argued higher TSH is simply a metabolic adaptation to obesity (5). Others have suggested obesity-related subclinical hypothyroidism (ScH), characterized by an increased serum thyrotropin (TSH) concentration with normal concentrations of the thyroid hormones, may be associated with dyslipidemia, insulin resistance, subclinical inflammation and increased risk for coronary heart disease (CHD) (6, 7). Even within the normal reference range for TSH, higher TSH has been linked to higher body mass index (BMI), dyslipidemia and fatal CHD (8-10). If an increased TSH in obesity is a risk factor, then thyroid hormone therapy in obese individuals with ScH to reduce TSH could be potentially beneficial, but this is controversial (5).

One of the potential causes of higher TSH concentrations in obesity is leptin, the adipocyte derived hormone that is increased with increasing body fat. In humans, direct correlations between TSH and leptin have been reported in cross-sectional and longitudinal studies (2). Leptin stimulates TSH production by the hypothalamic-pituitary axis in rats (11). At the same time, TSH may stimulate leptin production by adipocytes (12), suggesting cross-talk between these two hormones.

To clarify these issues, more data from prospective studies on the relationships between changes in thyroid function during weight loss, leptin, insulin resistance and other metabolic risk factors for CHD would be valuable. Such studies in obese children and adolescents may be particularly useful in that these relationships are less likely to be confounded by concurrent smoking, alcohol use, pharmacotherapy and/or chronic diseases. There is only one previous report in this age group; in obese German children in a 1 year outpatient program, weight loss significantly reduced TSH but changes in TSH were not associated with changes in lipids or insulin sensitivity (1). But only ≈20% of children successfully lost weight, and fat and lean tissue loss were not quantified.

Therefore, the aim of this study was to prospectively examine the associations between changes in thyroid function, leptin, insulin resistance and other metabolic risk factors for CHD in obese children and adolescents undergoing rapid weight and fat loss in a well-controlled, multidisciplinary, eight week inpatient program. We hypothesized that a greater decrease in TSH during weight loss would predict a greater decrease in insulin, LDL-cholesterol and triglyceride concentrations, independent of changes in body weight or body composition.

Subjects and methods

Subjects

The subjects were obese children and adolescents (n=206) aged 10-18 y enrolled in a multidisciplinary in-patient weight-loss program at the Alpine Children's Hospital in Davos, Switzerland. Inclusion criteria were a BMI over the 98th percentile for age and sex. Exclusion criteria were secondary obesity, (e.g. due to the Prader-Willi syndrome or underlying endocrine diseases; based on the medical history and/or clinical exam), type 2 diabetes and impaired glucose tolerance, or other major medical problems. The subjects were referred to the clinic by general pediatricians throughout Switzerland. Subjects and their parents or caregivers provided written informed consent. Ethical approval was obtained from the Canton of Graubünden Ethics Commission in Chur, Switzerland. Results on the effect of this program on body composition, aerobic fitness and quality of life in a subgroup and gender-specific differences have previously been described (13).Power calculations indicated 200 subjects should be studied to detect a TSH reduction of 10% (≈0.28 mU/l) considering a standard deviation of the TSH difference of 1.15 and with a power of 90% and a significance level of 0.05.

Study design

The treatment program consisted of moderate caloric restriction, daily physical activity and a behavior modification regimen (13). Baseline data were available for 206 subjects; 197 completed the 8-wk intervention.

Nutritional intervention. A 3-d food record was done at the beginning of the program to estimate the quality and quantity of the subject's usual diet. All children and adolescents received a nutritionally balanced diet, with the daily caloric intake during the program based on each patient's weight at baseline: weight <50 kg: 1200 kcal; weight 50-80 kg: 1400 kcal; and weight >80 kg: 1600 kcal. Five regular meals were given each day. The macronutrient composition was based on the recommendations of the Swiss Nutrition Society (www.sge-ssn.ch) and provided 55 to 60% energy as carbohydrates, 25-30% as fat and 15-20% as protein. Non-caloric drinks such as water and unsweetened tea were unrestricted. Nutritional education was provided to the subjects in weekly sessions: a 1-h group meeting, 30 min individual consultation and 2 h session with practical instructions in cooking and sensory aspects of food.

Physical activity program. The compulsory physical activity program included two daily group endurance exercise sessions to improve aerobic performance, with a typical session lasting 60-90 min. In addition, the subjects performed a weekly exercise session of 4-5 h (hiking, downhill skiing or snow shoe walking). During the exercise sessions, heart rate was controlled with heart rate monitors (Polar, S610 I, Polar Electro Europe, Zug, Switzerland) and maintained between 50 and 75% of maximal heart rate.

Behavior modification. Behavior modification focused on lifestyle issues with the aim of modifying eating and exercise behavior over the long term. The psychological intervention included self-monitoring of calorie intake, weight, praise and stimulus control, but also techniques focusing on increasing self-esteem, responsibilities and problem solving strategies. Relaxation techniques and breathing therapy were also used.

Study measurements

All anthropometric and biochemical measures were carried out at baseline and after eight weeks of intervention. Body weight was measured to the nearest 0.1 kg in the morning with the patients wearing light clothing and no shoes by using a electronic digital balance (Model 910, Seca, Reinach, Switzerland). Height was measured to the nearest 0.5 mm using a wall-mounted stadiometer (Model

222, Seca, Reinach, Switzerland). Body mass index was calculated as body weight in kilograms divided by height in meters squared. Body fat was measured using dual-energy X-ray absorption (DEXA) (Model 8743, Lunar Prodigy, GE Healthcare, Glattbrugg, Switzerland). Venous blood samples were obtained after a 10-hour overnight fast. Following blood sampling, the subjects underwent an oral glucose tolerance test and were given 1.75 g glucose/kg body weight (max. 75 g). Blood glucose concentration was determined after 1 and 2 hrs in a capillary blood sample.

Laboratory analysis

Insulin resistance was estimated by the homeostatic model assessment (HOMA-IR) as follows: HOMA-IR = [fasting insulin (µU/ml) × fasting glucose (mmol/l)/22.5] (14). Serum glucose was measured by UV-photometry (Architect Aeroset Glucose, Abbott Clinical Chemistry, Wiesbaden, Germany), total cholesterol, triglycerides, HDL- and LDL-cholesterol by enzymatic color reaction (Architect Aeroset Cholesterol / Triglycerides / Ultra HDL / LDL, Abbott Clinical Chemistry, Wiesbaden, Germany). Serum insulin, fT4, fT3 and TSH concentrations were measured by chemiluminescence (Architect System Insulin / Free T4 / Free T3 / TSH, Abbott Diagnostics Division, Wiesbaden, Germany), and serum leptin by radioimmunoassay (Human Leptin RIA Kit, Millipore (Linco), Molsheim, France). The reference range for TSH was 0.4-6.0 mU/l, and for fT3 and fT4 were 2.8-6.9 and 0.9-1.8 ng/dl, respectively. A TSH >2.5 and <6 mU/l was classified as high-normal (6).

Statistical analysis

The statistical analysis was done using SPSS for Windows (Version 17.0, Chicago, Illinois, USA) and Microsoft Office EXCEL 2007 (Redmond, Washington, USA). All data were controlled for normal distribution and non-normally distributed data were log-transformed prior to the analysis. For all biochemical parameters, relative differences (in % from baseline) were used to calculate a delta (Δ) value to take into account the different baseline concentrations. Similarly for the anthropometric parameters, relative values were used in order to take into account changes in body composition: % weight lost (% baseline weight - % endpoint weight), % fat lost (% difference from % values) and % lean tissue lost (% difference from % values). To compare BMI values across different ages and by

gender, BMI-standard deviation scores (SDS) were used. The standard deviation scores were calculated using the software Epi Info (version 3.5.1, Centers for Disease Control and Prevention (CDC)) based on the CDC recommendations 2000 (15). Differences in BMI-SDS between baseline and endpoint were calculated as absolute values. Paired samples t-test was used to analyze differences between baseline and after eight weeks of intervention. Univariate Pearson correlations were calculated to analyze associations between thyroid function parameters, weight status measures as well as components of the metabolic syndrome both for baseline data and for the changes after the intervention. Multiple regression models controlling for age, gender and body composition were used to better understand associations between thyroid function and components of the metabolic syndrome. The multiple regression models analyzing the changes during the intervention were also done using the relative differences for the metabolic parameters (baseline – endpoint). However, the results found were very similar to those using the relative differences and are therefore not shown. A p-value of <0.05 was considered significant.

Results

Table 1 shows the anthropometric and metabolic characteristics of the subjects at baseline (n=206) and after eight weeks (n=197). The intervention produced rapid loss of weight and fat: mean body weight and body fat were reduced by 14.4 kg and 8.7 kg, respectively, corresponding to a loss of 21% of body fat, while only 2.5% of lean tissue was lost. Insulin sensitivity sharply increased, as reflected in a >50% decrease in fasting insulin and HOMA. Circulating leptin concentrations decreased 76%. The lipid profile improved: there were significant decreases in triglycerides, total and LDL-cholesterol. There was a significant decrease in TSH and fT3 concentrations during the intervention, but no significant change in fT4. At baseline and endpoint, 107 and 87 of the subjects, respectively, had a TSH > 2.5 mU/l (high normal), while four and one, respectively, had a TSH > 6.0 mU/l (elevated). The children with an elevated TSH were not tested for thyroid antibodies, they were observed and not treated. At baseline, three subjects had low fT4 and none had a low fT3; after 8 wks, none of the subjects had an elevated fT3 or fT4. Baseline TSH was not significantly correlated with

either baseline fT3 (r=0.108, p=0.122) or fT4 (r=-0.070, p=0.318) but baseline fT3 was correlated to baseline fT4 (r=0.138, p=0.045).

Associations between variables at baseline

For baseline values, univariate correlations between weight status (body weight, BMI-SDS, fat mass, lean body mass and % body fat) and TSH, fT3 and fT4 were calculated. None of the five anthropometric indicators correlated with TSH. Body weight (p<0.001, r=-0.253), fat mass (p=0.002, r=-0.214) and lean body mass (p=0.004, r=-0.202) significantly negatively correlated with fT3, while BMI-SDS (p=0.010, r=0.181) and percentage body fat (p=0.003, r=0.211) positively correlated with fT4. However, in multiple regressions of the weight status indicators on fT3 or fT4 controlling for age and gender, none of the above associations remained significant. At baseline, in univariate correlations between TSH and variables of lipid and glucose metabolism, there were significant associations of TSH with triglycerides (r=0.142, p=0.043), total cholesterol (r=0.184, p=0.008), LDL-cholesterol (r=0.173, p=0.013), fasting insulin (r=0.181, p=0.010 (**Figure 1**), HOMA (r=0.200, p=0.004) but not HDL-cholesterol or 2-h glucose during the OGTT. fT3 and fT4 were not significantly correlated with any of these variables. Leptin was correlated with TSH (r=0.193, p=0.006) and fT3 (r= -0.214, p=0.002), but not fT4.

Table 2 shows the baseline multiple regression models of TSH as an independent variable on the variables of lipid and glucose metabolism, after controlling for each of three obesity measures individually (BMI-SDS, % body fat or lean body mass), along with age and gender. Total cholesterol, LDL-cholesterol, fasting insulin and HOMA significantly correlated with TSH even after controlling for all three measures of body composition. Triglycerides significantly correlated with TSH independent of % body fat, but not after controlling for BMI-SDS or lean body mass. HDL-cholesterol and the 2-h glucose during the OGTT did not correlate with TSH. If % body fat was replaced by body fat mass, the results of the regression were similar, except for the association with triglycerides, which was not significant (p=0.061). Baseline leptin was a significant predictor of baseline TSH after adjustment for age, gender and BMI-SDS (β=0.248, p=0.006), % body fat (β=0.330, p=0.001), body fat mass (β=0.284, p=0.002), and lean body mass (β=0.261, p=0.001).

Associations between variables during the intervention

Table 3 shows the univariate correlations during the intervention between loss of body weight and change in body composition and ΔTSH, ΔfT3 and ΔfT4. While ΔfT3 was significantly correlated with all four indicators of changes in body weight and composition, ΔTSH was not correlated with any of the changes in body weight or composition. ΔfT4 correlated only with % change in body weight. In univariate correlations between ΔTSH, ΔfT3 or ΔfT4 and the lipid variables, ΔTSH and ΔfT3 were predictors of ΔHDL-cholesterol (r=0.197, p=0.006 and r=-0.233, p=0.001) and ΔfT4 was a predictor of ΔLDL-cholesterol during the intervention (r=-0.157, p=0.028).

In multivariate models controlling for age, gender and Δbody weight or body composition, ΔTSH and ΔfT3 remained predictors of ΔHDL-cholesterol ($p<0.01$). ΔfT3 and ΔfT4 correlated with Δleptin (r=0.152, p=0.042 and r=-0.147, p=0.049) but were not predictors of Δfasting insulin or ΔHOMA. ΔTSH was a not a significant predictor of Δleptin. **Table 4** shows the significant multivariate associations between ΔTSH and Δfasting insulin and ΔHOMA during the intervention, while controlling for Δbody weight and Δcomposition, as well as age and gender. While ΔTSH significantly predicted Δfasting insulin (r=0.173, p=0.017, see **Figure 1**) and ΔHOMA (r=0.190, p=0.008), Δ body weight, fat or lean mass did not. The variance in ΔTSH explained 5-6% of the variance in fasting insulin and HOMA in all the models.

Discussion

Our study is the first to report changes in thyroid function tests and their relation to changes in lipid and glucose metabolism during an intensive, well-controlled inpatient intervention to achieve rapid weight loss in obese children and adolescents. Previous studies (1, 2, 16) have generally reported on smaller groups in less well-controlled, more heterogeneous, long-term outpatient interventions where weight loss is much more variable. Strengths of our study include: a) a large group of obese subjects who achieved substantial weight loss in a short time; b) a standardized in-patient intervention with similar dietary and exercise conditions applied to a relatively homogeneous group; c) measurements in

young subjects not confounded by chronic obesity-related disorders, smoking, alcohol, medications, etc.; d) measurement of changes in body composition using DEXA. Weaknesses of the study are the lack of a comparison group of normal weight children and the lack of thyroid antibody data from our subjects. However, in adults and children, thyroid autoimmunity does not appear to be increased in obesity (3, 17).

Because of varying TSH assays and cut-offs (18), it is difficult to directly compare results, but our data generally support previous studies that have reported higher TSH concentrations in obese subjects (3, 16, 17, 19). However, despite their severe obesity, TSH concentrations in our subjects were not markedly elevated (only 2% had an abnormally high TSH while 52% had a high-normal TSH) and there was very little evidence of thyroid hypofunction (only one child had a low fT4).

Although over half of these obese children had high-normal TSH values, baseline TSH or thyroid hormones were not correlated with body weight or body composition, after controlling for age and gender. Thus, although TSH concentrations tend to be higher in obese children, the elevations in TSH show inter-individual variability not explained simply by the amount of excess body weight or fat. Rather, our data suggest a close link between leptin and TSH in obese children, independent of body weight or fat: at baseline, leptin was a significant predictor of TSH after adjustment for age, gender and body weight and body composition. The lack of correlation between TSH and either fT3 or fT4 suggests normal feedback of TSH by circulating thyroid hormone is impaired in obese children and that high circulating leptin concentrations could play a role. The physiologic relationship between TSH and leptin is complex, in that leptin may have stimulatory or inhibitory effects on pituitary TSH secretion (11, 20, 21), but at the same time, TSH receptors are present in adipose tissue (22)and TSH may directly stimulate production of leptin by adipocytes (12).

Because TSH falls with weight loss in some studies (5) it has been suggested that higher TSH in obese subjects is simply a consequence of excess body fat. However, weight and/or fat loss does not predictably decrease TSH and T3 (1, 16, 19) and in our study, although there was a significant 11% decrease in overall mean TSH during the intervention, changes in TSH were not correlated with losses of weight, fat or lean tissue during the intervention. Other studies which did not find a decrease in TSH with weight loss suggested this could be explained by an inability to accurately quantify fat loss, rather than weight loss (1). An advantage of our study was use of DEXA to measure changes in body fat and lean tissue. Despite this, we were unable to find a clear relationship between changes in body composition and change in TSH.

It is unclear whether higher TSH in obesity is adaptive, increasing metabolic rate in an attempt to reduce further weight gain (5) or indicates subclinical hypothyroidism or resistance, and thereby contributes to lipid and/or glucose dysmetabolism. Our data, both at baseline and during the intervention, suggest the latter. At baseline, variation in TSH, but not variations in body weight or body fat, was a significant predictor of triglycerides, and total- and LDL-cholesterol. Both TSH (but not thyroid hormones) and body weight and composition were independent predictors of fasting insulin and HOMA, even though only 5-14% of their variation could be explained by the regression models (depending on obesity measure used in the model). The fact that baseline fasting insulin and HOMA are not associated with fT3 or fT3 and that baseline leptin is negatively associated with fT3 and not associated with fT4 further supports this hypothesis. Our data contrast with a previous study in obese adolescents, where no association was found between TSH and blood lipids (1). However, they are congruent with a larger cross-sectional study in adults which found clear associations between TSH concentrations within the normal range and lipid levels (9).

During the intervention, there was a >50% decrease in mean fasting insulin and HOMA. Strikingly, in multivariate regression models these improvements in insulin sensitivity were not predicted by changes in body weight, fat or lean mass, or changes in fT3, but rather by ΔTSH during the intervention (Table 5). Although only 5-6% of the variance in the change in fasting insulin or HOMA

during the intervention was explained by changes in TSH, this effect was clearly greater than the variance in these measures explained by changes in body weight or composition (all <1%, N.S.). Cross-sectional studies have reported associations between insulin resistance and TSH (23-25). But our prospective data are the first to demonstrate in children and adolescents undergoing weight loss that the resulting decrease in TSH, rather than changes in body weight or composition, is the main determinant of improvements in fasting insulin and HOMA.

Although our data are associations and do not prove causality, they suggest that interventions to decrease TSH concentrations during weight loss in obese subjects may be beneficial in further increasing insulin sensitivity. However, a recent systematic review concluded the available data do not support the use of thyroid hormone therapy in euthyroid obese subjects undergoing caloric deprivation (26); the authors suggested randomized placebo-controlled trials with relevant end-points and adequate power are needed to prove if there are beneficial effects of thyroid hormone in this setting (26). Our findings support this call for larger controlled trials, and suggest that measures of insulin sensitivity should be one of the relevant endpoints studied in such studies.

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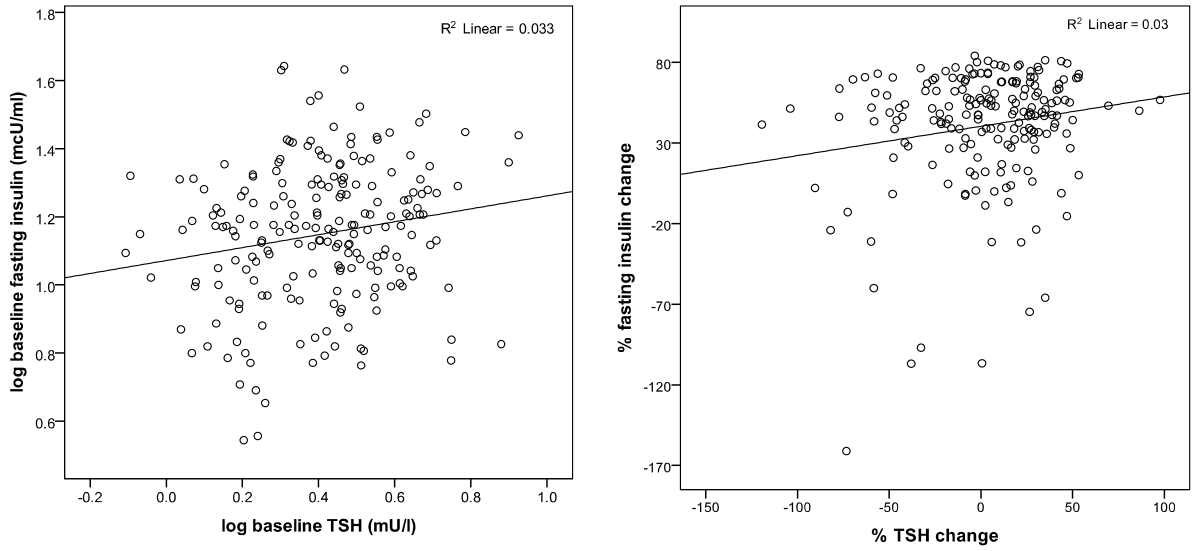

Figure 1. During an 8 wk, multidisciplinary inpatient weight loss program in obese children, there were significant correlations between; A) baseline concentrations of fasting insulin and TSH (p=0.010); and B) the percentage change (Δ) in fasting insulin and ΔTSH during the intervention (p=0.017).

Table 1: Characteristics of the study population

	Baseline	8 wk
N	206	197
Age	14.1 ± 1.9[1]	14.2 ± 1.9
Gender ratio (m:f)	119/87	117/80
Weight (kg)	93.8 ±20.5	79.4 ± 17.2[3]
BMI-SDS	2.28 ± 0.32	1.86 ± 0.43[3]
Body fat (kg)	41.6 ± 10.1	32.9 ± 10.0[3]
Lean tissue (kg)	49.0 ± 10.0	47.8 ± 9.7[3]
% body fat	46.8 ± 4.7	41.3 ± 6.0[3]
TSH (mU/l)	2.64 (0.78-8.42)[2]	2.36 (0.18-6.29)[3]
fT3 (ng/dl)	3.8 (2.9-5.7)	3.3 (1.7-4.5)[3]
fT4 (ng/dl)	1.2 (0.8-1.6)	1.2 (0.8-1.9)
Fasting insulin (U/ml)	14.7 (3.5-43.9)	7.1 (3.0-30.4)[3]
HOMA	3.0 (0.44-9.68)	1.4 (0.52-5.94)[3]
Triglycerides (mg/dl)	103.5 (30.0-354.0)	59.0 (23.0-195.0)[3]
Total cholesterol (mg/dl)	172.4 ± 36.7	123.9 ± 25.3[3]
HDL-cholesterol (mg/dl)	44.7 ± 8.8	43.5 ± 8.7[3]
LDL-cholesterol (mg/dl)	113.2 ± 31.3	69.6 ± 22.0[3]
Leptin (µg/l)	29.0 (4.0-89.0)	7.0 (1.0-29.0)[3]

[1] mean ± SD (all such values)

[2] median (range) (all such values)

[3] significantly different from baseline values (paired samples t-test, $p<0.05$)

HOMA was calculated as [fasting insulin (µU/ml) × fasting glucose (mmol/l)/22.5]

Table 2 Multivariate regressions of TSH (independent variable) on blood lipid concentrations and measures of insulin resistance (dependent variables) always controlling for one adiposity measure (BMI-SDS, % body fat (BF) or lean tissue mass (LTM)) together with age and gender

	Triglycerides		Total cholesterol		LDL-cholesterol		Fasting insulin		HOMA	
	β*	p	β	p	β	p	β	p	β	p
TSH (+ BMI-SDS)	0.132	0.057	0.179	0.011	0.158	0.025	0.148	0.027[1]	0.167	0.013[1]
TSH (+ % BF)	0.142	0.046	0.179	0.012	0.166	0.022	0.194	0.007	0.215	0.003
TSH (+ LTM)	0.133	0.056[1]	0.181	0.011	0.169	0.017	0.189	0.006[1]	0.210	0.002[1]

*standardized coefficient

[1] the obesity measure was a significant predictor as well ($p<0.05$)

Table 3 Univariate correlations between percentage differences (Δ) in TSH, free T3 and free T4 and percentage changes in weight, fat and lean tissue loss, as well as ΔBMI-SDS after 8 weeks of in-patient treatment of obese children and adolescents.

	Δ TSH abs		Δ T3 abs		Δ T4 abs	
	r*	p	r	p	r	p
% weight loss	0.103	0.148	0.088	0.222	-0.189	0.008
% fat loss	-0.071	0.329	0.280	<0.001	-0.081	0.267
Δ BMI-SDS	-0.072	0.321	0.320	<0.001	-0.112	0.121
% lean tissue loss	-0.028	0.706	-0.250	0.001	-0.011	0.876

* pearson correlation coefficients

Table 4 In an eight-week, inpatient weight loss intervention in obese children, multiple regression analysis with Δfasting insulin[1] or ΔHOMA as the dependent variable and including ΔTSH and either percentage loss of total body weight, body fat or lean tissue, with all models controlled for age and gender.

	Δ Fasting insulin		Δ HOMA	
	β [2]	p	β	p
Δ TSH	0.165	0.023	0.179	0.014
% weight loss	0.128	0.116	0.132	0.107
	R^2=0.062[3]		R^2=0.062	
Δ TSH	0.181	0.014	0.198	0.007
% fat loss	0.056	0.481	0.040	0.617
	R^2=0.050		R^2=0.048	
Δ TSH	0.181	0.013	0.198	0.007
% lean tissue lost	-0.118	0.122	-0.103	0.179
	R^2=0.060		R^2=0.057	

[1] For all metabolic parameters Δ values were calculated as relative differences (in % from baseline concentrations)

[2] standardized coefficient

[3] R^2 values of the entire model including TSH, change in body composition, age and gender